Remarks/Arguments

Claims 1, 4-9, and 15-16 are under examination. Claims 1-8 and 10-14 have been canceled. Claims 17-24 are added. Claims 17-20 restate the invention to more clearly define the meets and bounds of the method of the invention. Claims 22-24 are drawn to the targeting vector used in the method of the invention. Support for the new claims is found in the specification at paragraph 14, and original claims 4-8.

Claim 9 is amended in light of the Examiner's remarks. Support for the amendments to claim 9 can be found in Example 1 (p. 10). No new matter is introduced by the amendments and the Examiner is respectfully requested to enter these amendments. The following remarks address each rejection in the order it was made.

I. Rejections under 35 USC §112, first paragraph

Claims 1-16 were rejected for lack of enablement on the basis that the specification does not provide enablement for a method of generating drug resistant embryonic stem cell colonies and a method for targeting a targeting vector into an embryonic stem cell *in vivo*.

Claims 1-8 and 10-14 are canceled. These rejections are believed to be obviated by the amendment to claim 9 which recited an *in vitro* method, as does new claim 17. Accordingly, applicants respectfully request that this rejection be withdrawn.

II. Rejections under 35 USC §103(a)

Claims 1-16 were rejected as being unpatentable over Ghazizadeh *et al.* (1998) J. of Investigative Dermatology, 111:492-496 in view of Gill *et al.* (2001) Gene Therapy, 8:1539-1546. The rejection is respectfully traversed as it may be applied to the amended and new claims.

Obviousness is a legal conclusion based on underlying facts of four general types: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviouseness. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 15L. Ed. 2d 545, 86 S. Ct. 684 (1966); Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750-51 (Fed. Cir. 1991); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1594 (Fed. Cir. 1987). Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of

the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular resources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp., 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2D 1377, 1379 (FED. CIR. 1994)) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.")

The invention as claimed. The invention as claimed is drawn to *in vitro* methods of targeting a mouse embryonic stem (ES) cell through the introduction of a targeting vector comprising a ubiquitin promoter, and to methods of targeting a targeting vector into mouse ES cells through the introduction of a targeting vector comprising a ubiquitin promoter.

The Ghazizadeh *et al.* reference. Ghazizadeh *et al.* describe using a retrovirus vector comprising the lacZ gene and the neomycin phophotransferase gene to select non-transformed porcine keratinocytes using G418 to select cells which are not expressing neomycin phophotransferase.

Applicant submit that Ghazizadeh *et al.* do not disclose or suggest (1) using a targeting vector comprising a ubiquitin promoter (e.g., a vector that contains sequences homologous to endogenous chromosomal nucleic acid sequences flanking a desired genetic modification, see the instant specification at ¶ [0014]), and/or (2) targeted integration. Ghazizadeh *et al.* do not disclose a vector having sequences homologous to endogenous chromosomal nucleic acid sequences flanking a sequence targeted for a desired genetic modification. As is well known in the art, retroviral vectors randomly integrate sequences into a host chromosome. Thus, Ghazizadeh *et al.* teach random integration into a genome, not targeted integration.

The Gill et al reference. Gill *et al.* describe using the human ubiquitin C promoter results in significant increases in transgene expression compared to other promoters, such as CMV.

Gill *et al.* does not disclose or suggest (1) using a targeting vector comprising a ubiquitin promoter and/or (2) targeted integration. Gill *et al.* do not disclose using a targeting vector, nor does Gill *et al.* suggest using a targeting vector that comprises sequences homologous to endogenous chromosomal sequences flanking a site for a desired genetic modification. Instead, Gill *et al.* disclose transient transfection of mouse lung cells with plasmids or naked DNA. Accordingly, there is no guidance or motivation in Gill *et al.* that would lead a person of ordinary skill to the method of the rejected claims.

The analysis under §103(a). As shown by the above analysis, applicants respectfully submit that the examiner has failed to establish a *prima facie* case of obviousness because neither

cited prior art reference, alone or in combination, suggests generating drug resistance mouse ES cells or targeting mouse ES cells with a targeting vector comprising a ubiquitin promoter. Neither reference describes or suggests using a targeting vector that will lead to a targeted integration. The cited references disclose vectors that allow only *random* integration or transient (extrachromosomal) transgene expression.

Further, neither reference alone or in combination provide any guidance or motivation to generate a drug resistant mouse ES cell by introducing into the ES cell a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter. The cited references fail to even hint at any advantage to using a targeting vector to place a ubiquitin promoter in a genome. Thus, combining the cited references would not lead a person of ordinary skill to the instant claimed method.

Accordingly, in light of the above remarks, it is respectfully requested that this rejection be withdrawn.

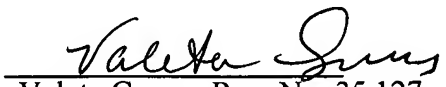
Conclusion

It is believed that this document is fully responsive to the Office action dated 5 October 2005. In light of the above amendments and remarks, it is believed that the claims are now in condition for allowance, and such action is respectfully urged.

Fees

Although it is believed that no fees are due, in the event the Patent Office determines that fees are due, the Commissioner is hereby authorized to charge Deposit Account Number 18-0650 in the amount of any fees deemed to be due.

Respectfully submitted,



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